2. The nucleic acid construct of claim 1, wherein the unmodified stem loop structures are unmodified U snRNA structures.

13. A method for suppression of gene expression in a cell comprising administering to [a] the cell a suppressive-effective amount of the nucleic acid construct of claim 1, whereby expression of the gene is suppressed in the cell.

REMARKS

The present invention provides a nucleic acid construct for delivery of antisense nucleic acid sequences to cells for suppressing gene expression and methods of using the construct to suppress gene expression. A construct, having an unmodified 5' stem loop structure and an unmodified 3' stem loop structure on either side of an antisense nucleic acid sequence, targets a complementary nucleic acid sequence, *i.e.*, a mRNA sequence, thereby inhibiting gene expression.

Claims 1 to 15 are pending. By the present communication, claims 1, 2 and 13 have been amended. No new matter is added by the amendment as the amendments are fully supported by the specification and originally filed claims.

Double Patenting

Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11 of U.S. Patent No. 5,814,500. As noted by the Examiner, Applicant will consider submitting a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) to overcome the rejection once pending claims are allowed.

Rejections Under 35 U.S.C. § 112

The rejection of claims 1-15 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement is respectfully traversed.

Applicant respectfully disagrees with the Examiner's assertion that the specification does not provide enablement for the breadth of nucleic acid constructs and methods instantly claimed. Applicant's invention, as defined by claim 1 and claims dependent therefrom, requires a nucleic acid construct for suppressing gene expression. The construct can be used in a method for the suppression of gene expression by administering the construct, in a suppressive-effective amount, to a cell to effect suppression of gene expression. The construct includes an unmodified 5' stem loop structure, an antisense nucleic acid and an unmodified 3' stem loop structure.

Support for the construct is provided in the specification. For example, support for stem loop structures is provided at page 7, line 12 to page 8, line 17 and support for antisense nucleic acids is provided at page 8, line 18 to page 10, line 2. Exemplary constructs of the invention are provided in the Examples section (page 23, line 6 to page 27, line 25). Accordingly, ample support for invention compositions, *i.e.,* delivery constructs for antisense nucleic acids is provided.

Furthermore, support for delivery of the invention construct used in a method for suppression of gene expression is provided. For example, delivery of invention construct may be achieved by colloidal dispersion systems such as liposomes (page 13, line 3 to page 14, line 2), by naked gene expression vectors (page 14, lines 3 to 7), and by viral vectors (page 16, lines 11 to 28). In particular, the specification teaches, as acknowledged by the Examiner, the use of one liposome formulation, *i.e.*, DOTAP liposome formulations, for the delivery of invention construct to cells. Results from

exemplary transfections of a human osteosarcoma cell line with invention constructs using the DOTAP liposome formulation are provided (page 25, line 21 to page 27, line 25).

In view of the ample guidance to make and/or use the invention provided in the specification, Applicant submits that the specification is fully enabling. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1 to 15 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102

The rejection of claims 1 to 12 under 35 U.S.C. § 102(a) as allegedly being anticipated by Michienzi *et al.* (Proc. Natl. Acad. Sci. USA, 993:7219 (1996)) is respectfully traversed.

The Office Action indicates that Michienzi *et al.* teach a U1 snRNA ribozyme construct for suppressing Rev gene expression in cells. Michienzi *et al.* teaches constructs that contain modifications in stem loop III of U1 snRNA. The modifications in a stem loop are schematically shown on page 7221, Figure 1, bottom left, where the modified regions appear in bold type. The location for modification was specifically chosen for several reasons delineated on page 7220, column 2, first paragraph. All the constructs taught by Michienzi *et al.* have modifications in the 5' stem loop. In contrast, Applicant's invention, as defined by claim 1, recites an unmodified 5' stem loop structure and an unmodified 3' stem loop structure.

Furthermore, in contrast to Applicant's invention, the constructs of Michienzi *et al.* are not designed to achieve an antisense effect. Indeed, the constructs were designed to "control for the antisense effect of ribozymes" (page 7220, column 2, paragraph 3). Therefore, Michienzi *et al.*

teaches away from the constructs of Applicant's invention which are designed to deliver an antisense composition to cells.

Accordingly. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

In view of the remarks herein, reconsideration and favorable action on all pending claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is requested to telephone Applicant's representative, Lisa A Haile, J.D., Ph.D., so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: **January 26, 2001**

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In re Application of:
Harry C. Dietz .
Application No.: 09/163,289
Filed: September 29, 1998
Exhibit A: Page 1

PATENT
Attorney Docket No.:07265/098002
(JHU1400-1)

Exhibit A: Claims Upon Entry of Amendments

1. (Amended) A nucleic acid construct for suppressing gene expression comprising:
an unmodified 5' stem loop structure;
an antisense nucleic acid; and
an unmodified 3' stem loop structure.

2. (Amended) The nucleic acid construct of claim 1, wherein the unmodified stem loop structures are unmodified U snRNA structures.

3. The nucleic acid construct of claim 2, wherein the U snRNA is U1.

4. The nucleic acid construct of claim 1, further comprising a promoter.

5. The nucleic acid construct of claim 4, wherein the promoter is a U1 snRNA promoter.

6. The nucleic acid construct of claim 4, wherein the promoter is a constitutive promoter.

7. The nucleic acid construct of claim 4, wherein the promoter is an inducible promoter.

8. The nucleic acid construct of claim 1, further comprising a ribozyme nucleic acid.

9. The nucleic acid construct of claim 8, wherein the ribozyme nucleic acid is located between the 5' and 3' stem loop structures.

10. The nucleic acid construct of claim 8, wherein the ribozyme nucleic acid is a hammerhead-type ribozyme.

11. The nucleic acid construct of claim 8, wherein a consensus sequence for ribozyme cleavage in a target nucleic acid is 5'-GUC-3' or 5'-GUA-3'.

12. The nucleic acid construct of claim 1, wherein the antisense nucleic acid is selected from the group consisting of rent-1, HPV E6, HIV, hyaluronic acid synthase, and fibrillin.

13. (Amended) A method for suppression of gene expression in a cell comprising administering to the cell a suppressive-effective amount of the nucleic acid construct of claim 1, whereby expression of the gene is suppressed in the cell.

14. The method of claim 13, wherein the administering is *ex vivo*.

15. The method of claim 13, further comprising administering a modified nucleic acid encoding a wild-type polypeptide corresponding to the gene product of the gene being suppressed, wherein the modified nucleic acid is resistant to ribozyme cleavage and/or antisense inhibition.